

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

<p>see form PCT/ISA/220</p>	SA/220	DATE	NTD
ANKOM 29 APR 2005 GIPS			

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**
(PCT Rule 43bis.1)

<p>Applicant's or agent's file reference see form PCT/ISA/220</p>	DATA ENTERED	FOR FURTHER ACTION See paragraph 2 below
FINAL CHECK		International filing date (day/month/year) 20.12.2004
		Priority date (day/month/year) 24.12.2003
International Patent Classification (IPC) or both national classification and IPC A61K31/505, C07D239/42, A61P35/00, C07D405/12, C07D417/12, C07D413/12, C07D401/12, C07D413/14,		
Applicant ASTRAZENECA AB		

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

<p>Name and mailing address of the ISA:</p> <p> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</p>	<p>Authorized Officer</p> <p>Seymour, L. Telephone No. +49 89 2399-8694</p> <p style="text-align: right;"></p>
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005332

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. **type of material:**
 - a sequence listing
 - table(s) related to the sequence listing
 - b. **format of material:**
 - in written format
 - in computer readable form
 - c. **time of filing/furnishing:**
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/005332

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,
 claims Nos. 16(part)

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the whole application or for said claims Nos. as above
- the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form has not been furnished does not comply with the standard
 - the computer readable form has not been furnished does not comply with the standard
- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/005332

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-16
	No: Claims	
Inventive step (IS)	Yes: Claims	1-16
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the International application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2004/005332

Re Item III

Present claim 16 relates to compounds defined by reference to process claim 15 in which it is stated that "any functional group is protected if necessary", and Lg^2 and Lg^3 are defined as "a suitable displaceable group". Whereas these terms are considered to be clear in the context of the particular reaction claimed, they lead to a lack of clarity (Article 6 PCT) in the compound claims, divorced from the corresponding reaction conditions. It is thus unclear which specific compounds fall within the scope of said claim. Consequently, the search of claim 16 did not include compounds wherein "any functional group is protected if necessary", and the meanings of Lg^2 and Lg^3 were restricted to the specific leaving groups listed as preferred embodiments in claim 15.

Re Item V

1. Reference is made to the following documents:

D1: WO 03/080064 A
D2: WO 03/080625 A
D3: WO 02/08205 A

2. Claims 1-16 meet the requirements of the PCT with respect to novelty (Article 33(2) PCT):

The region of overlap between present claims 1 and 16 and claim 1 of D3 can be regarded as a novel selection, since the former result from a choice of a particular combination of substituents from the general formula of D3, which is not specifically disclosed in the latter.

3. Claims 1-16 meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT):

The problem underlying the present application lies in the provision of further compounds having inhibitory activity for the Tie2 receptor tyrosine kinase and accordingly having value in the treatment of disease states associated with pathological angiogenesis.

Documents D1 and D2 disclose compounds having the same activity as the present compounds, where the main difference in structure lies in the replacement of the five-membered ring fused to the pyrimidinyl ring in D1 and D2 with an ethynyl linker. No incentive is provided in the prior art that would lead the person skilled in the art to perform this modification as a solution to the above-mentioned problem. It has been made credible that the claimed compounds solve the present problem (see present description, p. 85).

The intermediates of claim 16 share the structural element of formula I which makes the contribution over the prior art and are therefore also considered to be inventive.

Re Item VIII

1. Claim 16 is unclear because the compounds are defined by reference to process claim 15 containing functional definitions which are clear within the context of the process but not in the context of an independent compound claim (cf. Item III). It is also noted that the point of attachment of L (*meta* or *para*) is implicit in claim 15 (through the reference to claim 1), but is not clearly specified in claim 16, particularly for intermediate VIc.
2. Claim 10 is unclear (Article 6 PCT) owing to its reference to the description (see also Rule 6.2(a) PCT).
3. The optional features in the claim 15, i.e. the definitions following "for example", have no limiting effect on said claims (Article 6 PCT).